REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

At the outset, Applicants thank Examiners O'Hara, Seharasyon and Spector for the courtesy of the interview held on April 10, 2003, and their helpful comments.

I. STATUS OF THE CLAIMS

As correctly indicated in the Office Action Summary, claims 1-3, 5-7, 9-11, 13-15, 17-19, 21-23, 25, 26, 28-30, 32-34, 36-38, 40-42, 44-46 and 48 are pending and stand rejected.

By entry of this amendment, Applicants have canceled claims 2, 26, 28-30, 32-34, 36-38, 40-42, 44-46 and 48 without disclaimer to or prejudice of the subject matter contained therein. Applicants reserve the right to file a continuation or divisional application on the canceled subject matter.

Applicants introduce new claims 49-57 directed to methods of treating nucleus pulposus mediated disorders, which are supported at least in the original claims of the PCT application as well as throughout the specification. Applicants note that all the new claims are dependent on previously examined claims and therefore do not pose an undue burden on the Examiner by their addition. Claim 5 is further amended to recite "presents as sciatica" to more precisely claim the invention.

Applicants have amended claim 1 to more distinctly claim the subject matter of the claim pursuant to suggestions kindly provided during the interview. Applicants have amended claim 5 to depend from claim 1 and not claim 3.

II. STATUS OF THE APPLICATION

This application was withdrawn from allowance after payment of the issue fee. Applicants have not requested reimbursement of the issue fee and will request that the issue fee be applied to this application when allowed.

Applicants note the acknowledgment of foreign priority under 35 U.S.C. § 119(a)-(d) or (f) has been made and the certified copy of the two Swedish priority documents received.

Applicants respectfully request acknowledgment of the IDSs (Form 1449) submitted by Applicants on February 27, 2003.

Applicants note acceptance by the Office of the amendment to the title.

Applicants note that the rejections of (1) claims 27, 28, 31, 32, 35, 36, 39, 40, 43, 44, 47 and 48 under 35 U.S.C. § 112, second paragraph; (2) claims 27, 31, 39, 43 and 47 under 35 U.S.C. § 101; (3) claims 1-3, 5-7, 9-11, 13-15, 17-19, 21-23, 25, 26, 28-30, 32-34, 36-38, 40-42, 44-46 and 48 under 35 U.S.C. § 112, first paragraph; and (4) claims 1-3, 5-7, 9-11, 13-15, 17-19, 21-23, 25, 26, 28-30, 32-34, 36-38, 40-42, 44-46 and 48 under 35 U.S.C. § 103(a) over Wang *et al* (1996) in view of Xue *et al.* (U.S. Pat. No. 5,703,092) have been withdrawn.

III. SCIENTIFIC BACKGROUND ON NUCLEUS PULPOSUS MEDIATED DISEASE AND SCIATICA

An understanding of nucleus pulposus and how it acts to cause disorders is needed to distinguish the claimed invention from the prior art. One nucleus pulposus mediated disorder is sciatica. The word "sciatica" is derived from the Latin word "ischii" which means located in the region of the hip. The peripheral nerve that runs in the leg from the level of the pelvis down to the knee is called the "sciatic nerve". The pain associated with sciatica is typically felt in the hip, buttocks and/or leg. However, sciatica is not associated with peripheral nerves, including the sciatic nerve. Unfortunately, the radiating pain felt in the leg with sciatica was first considered to be local inflammation of the sciatic nerve,

hence the name "sciatica". Today, sciatica is known to be a problem linked to the intraspinal nerve root, which is not part of the peripheral nervous system and is not a peripheral nerve. Thus, although the term "sciatica" lives on, it is not at all related to the sciatic nerve, and the sciatic nerve has nothing to do with the condition of sciatica.

Sciatica and other nucleus pulposus induced nerve disorders cannot be classified as a neurodegenerative disorder. Neurodegenerative disorders are hereditary or sporadic conditions which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral nervous system, mainly the brain. Sciatica and nucleus pulposus induced conditions do not involve atrophy of the brain. Nucleus pulposus induced conditions are not hereditary, caused by a metabolic process, or caused by infection. Examples of neurodegenerative conditions include: motor neuron disease (*e.g.*, amyotrophic lateral sclerosis), Alzheimer's disease, and Parkinson's disease. Thus, neurodegenerative conditions clearly would not include nucleus pulposus induced disorders such as sciatica.

Instead, nucleus pulposus mediated disorders relates to intraspinal nerve root exposure to the nucleus pulposus. The presence of constriction or compression of the nerve is not required for the disorder to manifest itself. It was the discovery that exposure of the intraspinal nerve root to the nucleus pulposus material (*i.e.*, the jelly-like disk tissue) resulted in a reduction in motor nerve conduction in the **absence of mechanical compression** of the nerve. This reduction in motor nerve conduction is characteristic of sciatica and other nucleus pulposus mediated disorders. It is the contact with the jelly-like nucleus pulposus tissue, or components therein, which cause the disorder. No nerve compression, constriction, or nerve injury is necessary for reduction in motor nerve conduction velocity or to cause sciatica. In fact, exposure of a peripheral nerve to nucleus pulposus does not cause any irritation to the peripheral nerve. *See* Rydevik *et al.*, 1983, *Acta Orthop. Scand.* 54(4): 670-71 (attached).

Thus, none of the references cited by the Office relate to nucleus pulposus mediated disorder whatsoever, as the conditions discussed by the references do not involve any nerve root exposure to the nucleus pulposus jelly-like material.

IV. REJECTIONS UNDER 35 U.S.C. § 102(a)

The rejection of claims 1-3, 5-7, 9-11, 13-15, 17-19, 21-23, 25, 28, 32, 36, 44, and 48 under 35 U.S.C. § 102(a) as purportedly anticipated by Sommer *et al.*, 1997, *Neuroscience Lett.* 237:45-48 (hereinafter "Sommer") has been reinstated as presented in Paper No. 13 mailed May 21, 2002. The Office alleges that the method of treatment is inherently the same as that described in the art. The Office cites a second reference in the § 102(a) rejection (*i.e.*, Olmarker *et al.*, 1994 Spine 19(16): 1803, 1808, hereinafter "Olmarker"). Specifically, Olmarker is alleged as suggesting that inflammatory mechanisms to be of pathogenetic significance in disc herniation with sciatica. It is further asserted that "Applicant's apparent elucidation of an underlying mechanism or mode of action for known compounds does not make the method of treatment using the same, patentably distinct."

1. The Teachings of Sommer *et al.* (1997)

Applicants respectfully disagree and assert that no *prima facie* case of anticipation has been set forth by the Office.

To anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984).

Sommer does not teach explicitly or inherently the claimed method or compositions. Sommer teaches the mechanical deformation by ligation of a nerve until brief twitch in the hind limb of a mouse. The ligated nerve is the sciatic nerve. Sommer at 46. The sciatic

nerve is a peripheral nerve. As discussed in Section IV, the sciatic nerve is not involved in sciatica or nucleus pulposus mediated disorders. These disorders involve nerve roots, which are anatomically quite different than the peripheral nerves. Additionally, sciatica and other nucleus pulposus mediated disorders can occur in the absence of any ligation or mechanical constriction of a nerve. The pathology of sciatica and nucleus pulposus mediated diseases, as discussed in Section IV, is caused by a different mechanism than the experimental model proposed by Sommer or the other diseases listed by Sommer (*e.g.*, constrictive mononeuropathies, nerve crush, chronic constriction nerve injury (CCI), experimental autoimmune neuritis or lepromatous leprosy). As no mechanical deformation of the sciatic nerve is needed for a nucleus pulposus mediated disorder, Sommer does not teach such disorders, let alone provide a method of treating them.

Finally, Sommer only teaches epineurial administration of drugs. *Id.* at 47, col. 2. Epineurial injection is not the same as systemic, oral, intramuscular or intravenous administration. Sommer does not suggest let alone teach other methods of administration. Clearly, there can be no motivation to combine the teachings of Sommer with Amin to administer the drugs in the manners suggested by the Office, as Amin specifically argues that TNF-α inhibitors would not be used to treat neurodegenerative disorders. Although Amin does teach alternative methods of administration, the skilled artisan would not consider that helpful given how Amin teaches away from the claimed invention and does not relate to or suggest nucleus pulposus disorders. Moreover, Sommer also does not teach methods of treating nucleus pulposus mediated disorders.

As discussed above, to constitute an anticipatory reference, all the elements must be set forth in the reference. As not all of the elements are taught or even suggested (*e.g.*, the condition being treated and the method of administering the drug for the condition being treated), the reference fails to be anticipatory.

2. References Do Not Inherently Teach The Claimed Invention

Turning to the allegation that Sommer inherently teaches the claimed invention, it does not. An anticipatory reference must teach every element of the claimed invention, as discussed above. The law permits, however, the use of extrinsic evidence to interpret or explain the disclosure of a prior art reference whose anticipatory effect is otherwise ambiguous. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991). Such evidence may only be used to explain the meaning the reference would have had to the person of ordinary skill in the art, but may not be used to "expand" or fill gaps in the teachings of the reference. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA Inc. v. Monsanto Co.*, 20 U.S.P.Q.2d 1747, 1749 citing to *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Sommer fails for the reasons noted in Section (1) above. The defects regarding the elements found lacking in Sommer cannot be compensated by any **extrinsic evidence** for purposes of a rejection under 35 U.S.C. § 102. The Olmarker reference can only serve to demonstrate that the allegedly inherent subject matter is in fact present. It cannot serve to teach missing subject not inherent to the primary reference. Thus, Olmarker cannot serve as a means of curing the defects of Sommer. Accordingly, no *prima facie* case of anticipation has been met by the Office, and the rejection should be withdrawn. Applicants respectfully request allowance of the claims.

V. REJECTIONS UNDER 35 U.S.C. § 103(A)

1. Rejection over Sommer (1997) in view of Xue

The rejection of claims 2-3, 5-7, 9-11, 13-15, 17-19, 21-23, 25, 26, 28-30, 32-34, 36-38, 40-42, 44-46, and 48 under 35 U.S.C. § 103(a) is reinstated as purportedly unpatentable over Sommer *et al.* (1997) in view of Xue *et al.* (U.S. Pat. No. 5,703,092 hereinafter "Xue").

Applicants respectfully traverse the rejection and assert that no *prima facie* case of obviousness has been adduced. Sommer is cited by the Office for the reasons discussed above. Sommer fails to teach or suggest the claimed invention for the reasons discussed above. The defects of Sommer are not cured by Xue as discussed below.

Xue is cited "primarily . . . to teach the various methods of administration". Office Action, page 4. The Office further asserted that "inhibiting the functionally active TNF-α in the treatment of nerve disorders or immune diseases was recognized in the prior art and Sommer *et al.* (which is not true as discussed in Sections III and IV). Thus, one skilled in the art would have been motivated to modify the methods disclosed in Sommer *et al.* using the teachings of Xue *et al.* to treat nerve disorders by using metalloproteinase inhibitor to inhibit TNF-α." Applicants assert that the reasoning used to achieve the conclusion is wrong and therefore the conclusion reached is wrong.

To establish a *prima facie* case, the Office must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain **some suggestion or incentive** that would have **motivated** the skilled artisan **to modify** a reference or to combine references. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a **reasonable expectation of success**, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art reference or combination of references must **teach or suggest all** the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). And the teachings or suggestions, as well as the expectation of success, must come from the prior art, not applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

Applicants assert that (1) there is no suggestion or incentive to modify the references, (2) the combination of the references do not teach all the elements of the

claimed invention, and therefore there can be no expectation of success. Sommer fails to teach a method for treating a nucleus pulposus mediated disorder for the reasons discussed above. There is no motivation to combine Xue with Sommer for purposes of administering the drug via the methods taught by Xue, as Sommer does not suggest a method to treat the disorder claimed by Applicant or provides a composition for use therefor. As conceded by the Office, Xue does not teach treatment of nerve disorders let alone nucleus pulposus mediated disorders or sciatica. Office Action, page 4. As the conditions discussed in Sommer are pathologically distinct from nucleus-pulposus induced conditions, a conclusion cannot be reached that "inhibiting the functionally active TNF-α in the treatment of nerve disorders or immune diseases was recognized." *Id.*

Furthermore, the conclusion reached by the Office is a broad brush generalization that all neural disorders are the same pathologically and would be treatable in the same fashion. As discussed during the interview, peripheral nerves are anatomically quite different than the nerve roots being treated in the instant invention. This is evidenced by the attached Abstract (Rydevik *et al.*, *Acta Orthop. Scand.* 54(4): 670-71), which clearly shows that exposure of a peripheral nerve to nucleus purposes does not lead to nerve irritation. This result is in stark contrast to the impact of nerve root exposure to one nucleus pulposus as discussed in the specification. Clearly, the methods of Xue do not compensate for the defects of Sommer. Accordingly, the combination of the reference do not serve to form a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the rejection in view of the arguments above and allowance of the claims.

2. Rejection over Sommer (1997) in view of Amin

Claims 2-3, 5-7, 9-11, 13-15, 17-19, 21-23, 25, 26, 28-30, 32-34, 36-38, 40-42, 44-46, and 48 stand newly rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Sommer *et al.* in view of Amin *et al.* (U.S. Patent No. 6,319,910, hereinafter "Amin").

Applicants respectfully traverse the rejection and assert that no *prima facie* case of obviousness has been adduced. Sommer is cited by the Office for the reasons discussed above. Sommer fails to teach or suggest the claimed invention for the reasons discussed above. The defects of Sommer are not cured by Amin. Thus, the references when viewed alone or in combination do not teach or suggest the claimed invention.

Amin purportedly discloses "that chemically modified tetracyclines, including doxycycline, are a class of non-steroidal anti-inflammatory drugs which inhibit TNF-α, and can be used for treating diseases or disorders associated with elevated activities of TNF-α." Amin also purportedly discloses "an effective amount of a chemically modified tetracycline used in a method for treating a disease or disorder associated with elevated levels of TNF-α, including neurodegenerative disorders . . . . that the active principal may be administered by any means that achieves the intended purpose such as parenteral routes, and that the dosage administered will be dependent upon the age, sex, health and weight of the recipient, kind of concurrent treatment, frequency of treatment and nature of the effect desired . . . ."

The Office sets forth that it "would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the methods disclosed in Sommer et al. to treat neurological conditions by administering TNF-α inhibitor containing pharmaceutical composition to a human as described by Amin *et al.*" The Office further asserts that since "Sommer *et al.* teach that in experimental neuropathies results in increased levels of TNF-α inhibitors, and since many nerve disorders such as spinal cord injury result in inflammation and increase in TNF-α, the skilled artisan would be motivated to treat any of these nerve disorders/injuries with the methods of Amin *et al.*"

As discussed above, Sommer does not teach or suggest the claimed invention. The patent issued to Amin does not cure these defects and in fact teaches away from the claimed invention. Additionally, Applicants assert that the conclusions reached in the Office Action are scientifically incorrect and as are the conclusions drawn therefrom.

First, a reference must be read for what it teaches as a whole and not for what it teaches in isolation. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). Amin is asserted as teaching an effective amount of a chemically modified tetracycline to treat a disease or disorder with elevated levels of TNF-α, including neurodegenerative disorders. Applicants assert that treatment of neurodegenerative disorders with TNF-α inhibitors is not taught. Within the text cited by the Office states the following:

> Non-limiting examples of **diseases and disorders associated with enhanced COX-2 activity** and elevated levels of COX-2 products treatable by the method of the present invention include brain ischemia, inflammatory bowel disease, **neurodegenerative disorders**, and cancers such as adenomatous polyposis, colon cancer, breast cancer and prostate cancer, etc. Non-limiting examples of **diseases and disorders associated with elevated levels of TNFα** treatable by the method of the present invention include multiple sclerosis, septic shock, periodontal disease, graft-vs.-host disease, cerebral malaria and cachexia associated with cancer or HIV infection. Accordingly, the method of the present invention can be used to prevent, inhibit, or alleviate such COX-2 and/or TNFα-related conditions. (Emphasis added). Col. 6, ll. 18-31.

Thus, neurodegenerative disorders are linked to COX-2 activity and not with TNFα activity. Therefore, the scientific conclusion regarding neurodegenerative disorders is wrong. Amin clearly teaches the use of COX-2 inhibitors and not TNFα inhibitors to treat neurodegenerative disorders. Therefore, if the assumption was correct that nucleus pulposus mediated condition is a type of neurodegenerative disorder (which it is not), Amin would teach away from using a TNFα inhibitor and teach the use of a COX-2 inhibitor. However, as discussed in Section III, neurodegenerative disorders involve atrophy, most typically of the brain. Nucleus pulposus mediated disorders are not localized in the brain. Additionally, there is nothing in Amin's list of disorders to be treated with TNF-α

inhibitors which would suggest the treatment of any nerve disorders, let alone a nucleus-pulposus mediated disorder or sciatica.

Amin further teaches away from the claimed invention based on its discussion relating to nitric oxide ("NO"). Amin teaches that the methods and compositions disclosed are for use in treating diseases and disorders wherein TNFα and/or the products of COX-2 are elevated, but not the level of NO. Col. 6, ll. 15-18. It is known that the level of NO is increased in the spinal nerve root tissue after exposure to nucleus pulposus. M. Kawakami *et al.*, 1999 *J. Bone & Joint Surgery* 17:941-46 (attached). Accordingly, a nucleus pulposus mediated disorder would result in both increased NO and an introduction of TNFα. Therefore, Amin teaches away from treating these disorders with TNFα or COX-2 inhibitors.

As Amin teaches away from claimed invention, there certainly would be no motivation to combine the teachings with Sommer. Additionally, Amin does not serve to teach anything relating to any nerve disorder, let alone a nucleus pulposus mediated disorder. Accordingly, Amin cannot serve to cure the defects found in Sommer. Sommer fails to teach the claimed invention as previous stated. As the combination of references does not constitute a *prima facie* case of obviousness, the rejection should be withdrawn and the claims allowed.

3. Assertion of Inherent Obviousness

The Office further states that "[a]lthough nucleus pulposus-induced nerve injury may not have been disclosed in the prior art, the method of treatment using TNF-α inhibitors is the same. Elucidation of an underlying mechanism does not make the method of treatment patently distinct." Office Action, page 6. This appears to be an inherency argument. Inherence arguments under 35 U.S.C. § 103 are improper. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency . . . may not be established by

probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999). That which is inherent in the prior art, if not known at the time of the invention, cannot form a proper basis for rejection the claimed invention as obvious under § 103. *In re Shetty*, 566 F.2d. 81, 86, 195 U.S.P.Q. 753, 756-57 (C.C.P.A. 1977). Stated differently, an "expectation of success" (an element which must be met for a combination of prior art to render an invention obvious) is a statement of a probability, and a probability cannot be used to establish inherency.

It is clear from the arguments present above, that Xue, Amin and Sommer do not teach anything explicitly or inherently with respect to methods of treating nucleus pulposus mediated disorders, let alone that TNF-α are or could be useful in treating such disorders. Accordingly, no *prima facie* case of obviousness has been adduced. The rejections under 35 U.S.C. § 103 should therefore be withdrawn and the claims allowed.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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